

tervention: the need to reevaluate our approach. *Arch Intern Med.* 2012;172(6):508-509.

The Big Ones That Got Away: Omega-3 Meta-analysis Flawed by Excluding the Biggest Fish Oil Trials

Kwak et al^{1(p686)} state that “Our meta-analysis showed insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements against overall cardiovascular events among patients with a history of cardiovascular disease.” We respectfully disagree with this conclusion. This meta-analysis mainly included trials comprising only 50 to 550 patients with just 2 years or less of follow-up (the point at which the survival curves started to diverge in the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico [GISSI] Heart Failure study²) in 10 of the 14 trials. In addition, 5 of the 14 trials were, in fact, not truly placebo controlled but used olive oil as a comparator. Kromhout et al³ used omega-3 fatty acids in margarine spread over multiple pieces of toast per day, which could nullify any beneficial effects of fish oil. Most included trials were not powered to detect a difference in cardiovascular outcomes (OMEGA⁴ and the SU.FOL.OM3 [Supplémentation en Folate et Omega-3]⁵ studies had approximately 20% power to detect a 25% benefit of omega-3 and the Alpha Omega study³ [used just 380 mg/d of eicosapentaenoic acid + docosahexaenoic acid] had approximately half the statistical power as the GISSI-Prevenzione study⁶). Thus, a “lack of inclusion of sufficient trial data” should not be interpreted as “insufficient evidence at preventing cardiovascular events.”

Excluded trials such as Diet and Reinfarction Trial (DART),⁷ which randomized 2033 men after myocardial infarction to fatty fish or 3 g of fish oil, showed a significant 29% reduction in 2-year all-cause mortality compared with those not so advised ($P=.05$) and a 16% reduction in the risk of ischemic heart disease events. The GISSI-Prevention trial⁶ randomized 11 324 patients after myocardial infarction to 1 g of omega-3 fatty acids for 3.5 years, which significantly lowered the risk of the primary end point (15% risk reduction in nonfatal myocardial infarction, death, and stroke as well as significant reductions in the risk of death [20%], cardiovascular death [30%], and sudden cardiac death [45%]). The Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS)⁸ was a randomized, blinded end point trial in 18 645 patients assigned to 1.8 g of eicosapentaenoic acid for 4.6 years. Omega-3 fatty acids caused relative risk reductions of 19% and 24% in major coronary events and unstable angina, respectively. Furthermore, nonfatal coronary events were significantly lower in the eicosapentaenoic acid group compared with placebo.⁸

In conclusion, the meta-analysis performed by Kwak et al¹ is significantly flawed by inclusion of negative poor quality, short-term studies, while excluding positive larger and longer-term studies. We

believe that the findings of this meta-analysis should be interpreted with caution.

James J. DiNicolantonio, PharmD
James H. O’Keefe, MD
Carl J. Lavie, MD

Author Affiliations: Department of Pharmacy, Wegmans, Ithaca, New York (Dr DiNicolantonio); University of Missouri–Kansas City School of Medicine, Kansas City (Dr O’Keefe); and Department of Cardiology, Ochsner Medical Center, New Orleans, Louisiana (Dr Lavie).

Correspondence: Dr DiNicolantonio, Department of Pharmacy, Wegmans, 500 S Meadow St, Ithaca, NY 14850 (jjdnicol@gmail.com).

Financial Disclosure: None reported.

1. Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med.* 2012;172(9):686-694.
2. Tavazzi L, Maggioni AP, Marchioli R, et al; GISSI-HF Investigators. Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2008;372(9645):1223-1230.
3. Kromhout D, Giltay EJ, Geleijnse JM; Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med.* 2010;363(21):2015-2026.
4. Rauch B, Schiele R, Schneider S, et al; OMEGA Study Group. OMEGA, a randomized, placebo-controlled trial to test the effect of highly purified omega-3 fatty acids on top of modern guideline-adjusted therapy after myocardial infarction. *Circulation.* 2010;122(21):2152-2159.
5. Galan P, Kesse-Guyot E, Czernichow S, Briancon S, Blacher J, Hercberg S; SU.FOL.OM3 Collaborative Group. Effects of B vitamins and omega 3 fatty acids on cardiovascular diseases: a randomised placebo controlled trial. *BMJ.* 2010;341:c6273.
6. Marchioli R, Schweiger C, Tavazzi L, Valagussa F; Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. *Lipids.* 2001;36(suppl):S119-S126.
7. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet.* 1989;2(8666):757-761.
8. Yokoyama M, Origasa H, Matsuzaki M, et al; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369(9567):1090-1098.

In reply

We appreciate the letter of DiNicolantonio et al in response to our report¹ in the Archives. We acknowledge that several methodologic issues raised by DiNicolantonio et al are important for our main conclusions.

First, regarding the small sample size and short follow-up period, we stated in the limitations of the “Comment” section^{1(p693)} that

Fifth, most trials included in the present meta-analysis had a small sample size of 59 to 500 participants and a short duration of treatment of less than 2 to 3 years. Further larger trials are needed.

However, although we included trials with a small sample size of participants, the number of total participants in the meta-analysis was more than 20 000, which is regarded as having enough power to detect a difference in cardiovascular outcomes.

Second, regarding the exclusion of the 5 trials with the use of olive oil as a control group, when we performed a sub-

group meta-analysis with excluding those 5 trials, no preventive effect of omega-3 fatty acid supplementation on overall cardiovascular events was observed (relative risk [RR], 0.94; 95% CI, 0.83-1.07). Also, when we performed a meta-analysis without the trial by Kromhout et al² that used margarine spread, there was no preventive effect (RR, 0.98; 95% CI, 0.86-1.11).

Third, the Diet and Reinfarction Trial (DART)³ that DiNicolantonio et al mentioned is not a relevant trial for our meta-analysis because it used only advice on an increase in fatty fish intake, not omega-3 fatty acid supplementation.

Last, regarding the exclusion of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione⁴ and Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS)⁵ in our analysis, we already addressed in the "Comment" section. Again, the main reason that we excluded those 2 large randomized controlled trials is that they used an open-label design without using placebos, which is liable to performance bias. For the readers who have the same question, in our article^{1(p691)} we already mentioned that

When we performed a meta-analysis with the GISSI-Prevenzione trial⁴ and the JELIS⁵ in addition to the 14 trials included in the present study, a preventive effect of omega-3 fatty acid supplementation was not observed (RR, 0.95; 95% CI, 0.87-1.03; $I^2=35.5\%$) (data not shown).

In conclusion, despite some methodologic issues and limitations, our meta-analysis indicates that there is a lack of sufficient evidence of the secondary preventive effects of omega-3 supplementation on cardiovascular disease. Further larger randomized, double-blind, placebo-controlled trials are needed to confirm our findings.

Sang Mi Kwak, MD
Seung-Kwon Myung, MD

Author Affiliations: Health Screening Center, Kangbuk Samsung Hospital, Sungkyunkwan University, School of Medicine, Seoul, Republic of Korea (Dr Kwak); and Carcinogenesis Branch, Family Medicine Clinic, and Center for Cancer Prevention and Detection, Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea (Dr Myung).

Correspondence: Dr Myung, Carcinogenesis Branch, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang, Gyeonggi 410-769, Republic of Korea (msk@ncc.re.kr).

Financial Disclosure: None reported.

1. Kwak SM, Myung SK, Lee YJ, Seo HG; Korean Meta-analysis Study Group. Efficacy of omega-3 fatty acid supplements (eicosapentaenoic acid and docosahexaenoic acid) in the secondary prevention of cardiovascular disease: a meta-analysis of randomized, double-blind, placebo-controlled trials. *Arch Intern Med.* 2012;172(9):686-694.
2. Kromhout D, Giltay EJ, Geleijnse JM; Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med.* 2010;363(21):2015-2026.
3. Burr ML, Fehily AM, Gilbert JF, et al. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). *Lancet.* 1989;2(8666):757-761.
4. Marchioli R, Schweiger C, Tavazzi L, Valagussa F; Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. Efficacy of n-3 polyunsaturated fatty acids after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico. *Lipids.* 2001;36(suppl):S119-S126.
5. Yokoyama M, Origasa H, Matsuzaki M, et al; Japan EPA lipid intervention

study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. *Lancet.* 2007;369(9567):1090-1098.

Antipsychotic Drugs and Myocardial Infarction in Patients With Dementia

Pariante et al¹ conducted a retrospective study of prescription claims data and found that, in elderly patients receiving anticholinesterase medications, antipsychotic dispensing was associated with an increased risk of myocardial infarction only during the first 2 months following antipsychotic initiation; in matched cohort and self-controlled analyses, there was no statistically significant elevation in infarction risk during subsequent periods, extending to a year after antipsychotic initiation and beyond.

Protopathic bias was briefly considered as an explanation for the initial risk¹; otherwise, the clinical significance of the lack of later risk was not addressed in either the main article¹ or the accompanying commentary.² This is surprising because the finding actually implies possible cardiovascular safety of antipsychotic medication in dementia. After all, if antipsychotic medication truly elevates cardiovascular risks, the effects should be uniform across time or cumulative, rather than only during the initial phase of treatment.

If antipsychotics truly raise cardiovascular risks at all periods, an explanation for the apparent late safety is that patients at high risk may not survive to contribute to the risk in later exposure periods. *Importantly, instead,* antipsychotics may truly be associated with only an initial risk and with an absence of risk during later periods. This can happen if the indications for which they are prescribed (eg, psychotic symptoms) are associated with state-dependent cardiovascular risk factors (eg, agitation), which attenuate or disappear (eg, because of antipsychotic treatment) in later months. If so, antipsychotic use may merely be a marker for the presence of cardiovascular risk factors and not the reason for infarction; alternately, antipsychotic medication may interact with state-dependent risk factors through an unknown mechanism to trigger a cardiovascular event. Either way, prospective studies should examine whether state-dependent risk factors exist and whether such risk factors are modifiable. Positive results could pave the way for the safer use of antipsychotic medication for acute indications in dementia.

Chittaranjan Andrade, MD
Praveen Paul Fernandes, MD

Author Affiliations: Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Bangalore India (Dr Andrade); and Department of Psychiatry, Creighton University School of Medicine, Omaha, Nebraska (Dr Fernandes).

Correspondence: Dr Andrade, Department of Psychopharmacology, National Institute of Mental Health and Neurosciences, Hosur Road, Bangalore 560029, India (andrdec@gmail.com).